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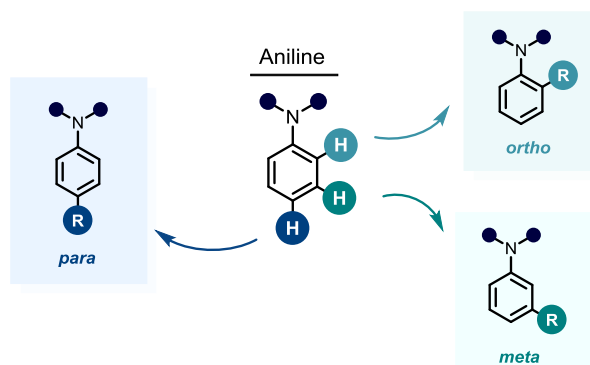
Regioselective Transition Metal Catalyzed C-H Functionalization of Anilines

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Abstract Anilines are a vital synthetic core of pharmaceuticals, agrochemicals, natural products and building blocks. Metal-catalyzed C-H functionalization has emerged as a powerful tool to derivatize biologically relevant molecules. To this end, the derivation of anilines via catalytic C-H functionalization has been the subject of important new synthetic methodology. This review focuses on the tactics used to allow regioselective C-H functionalization of anilines.

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Key words C-H Functionalization, Homogeneous Catalysis, Aniline, Regioselectivity, Aromatic

1. Introduction

Anilines are a ubiquitous chemical structure in a variety of active pharmaceuticals, agrochemicals, and natural products.¹ As per the Top 200 Pharmaceutical Product by Retail 2016, they are present in 16 active structures.² They are commonly found in oncology agents (imatinib, enzalutamide, nilotinib, erlotinib, Figure 1a), as well as cardiovascular treatments (rivaroxaban, ranolazine), and respiratory disorders (formoterol, ivacaftor). They have also been abundant

architectures in agrochemical development spanning a variety of pesticides (Figure 1b, flumetsulam, metolachlor, iprodione, and fluazuron).

These structures contain substitution patterns at the *ortho*, *meta* and *para* positions. For these reasons, regioselective C-H functionalization of aniline derivatives could provide a key avenue into late stage modification of biologically relevant structures or in the synthesis of intermediary building blocks.³ Transition metal-catalyzed C-H functionalization has emerged as a useful tool in the diversification of arenes and heteroarenes. The inherent challenge in C-H functionalization is the differentiation of sterically and electronically similar C-H bonds in an organic structure.⁴ For these reasons, elegant techniques have been designed to enable selective C-H functionalization methodologies. The use of a metal-coordinating directing group has emerged as the most studied method in enabling site selective C-H activation *via* chelation assistance.⁵ This concept has developed rapidly to the use of a variety of strongly and weakly coordinating directing groups, utilizing a multitude of metal systems.

Chelation assistance has enabled site selective C-H functionalization primarily at the *ortho* position of an arene. The first section of this review will focus on the variety of directing groups and systems that have permitted *ortho*-functionalization of aniline derivatives (Scheme 1).

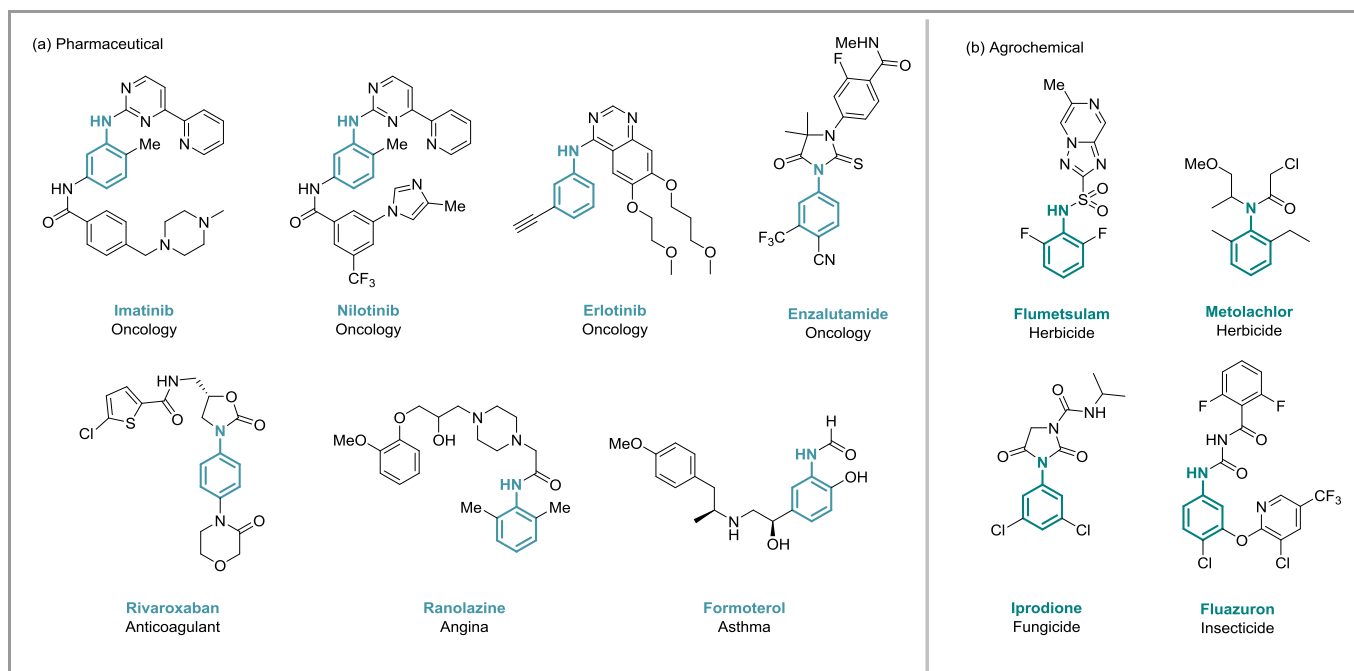
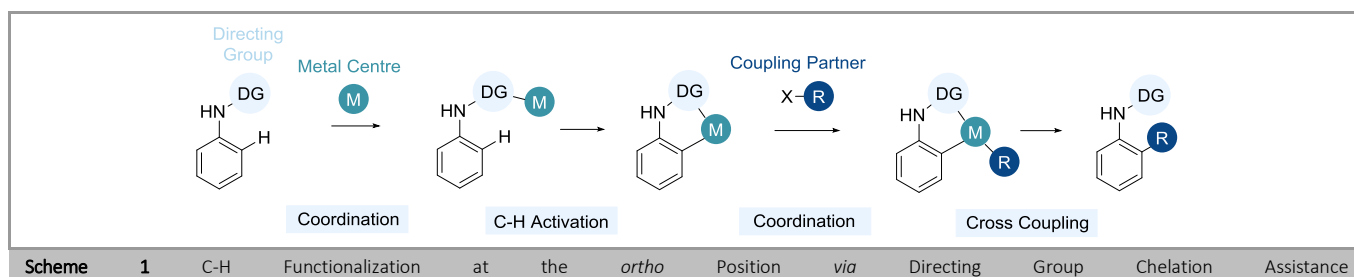


Figure 1 Biologically Relevant Aniline Structures

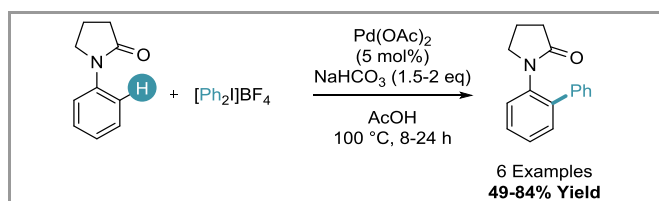


2: Ortho-Selective C-H Functionalization

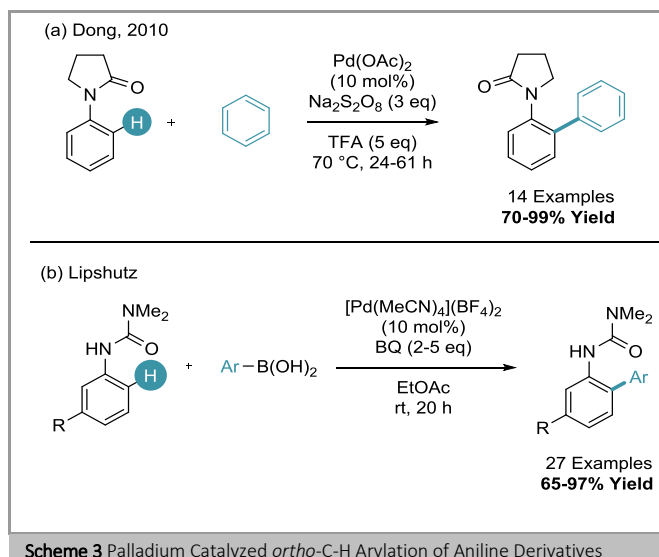
2.1: Palladium

The use of palladium catalysis in C-H functionalization chemistry has become widespread due to the innate reactivity of palladium centres. They have been shown to undergo direct C-H activation and functionalization of electronically biased systems,⁶ as well as undergo directed C-H functionalization, enabled *via* chelation assistance.⁷

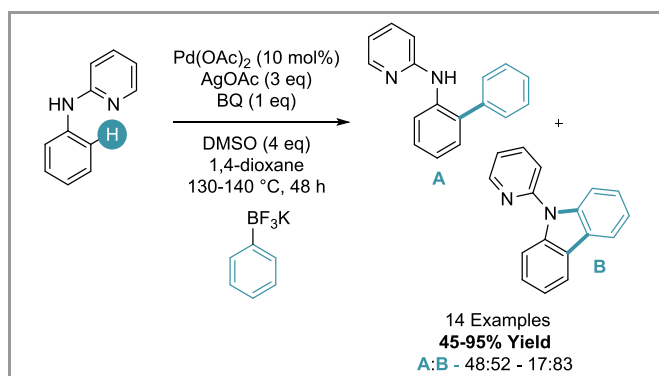
In early 2005, Sanford reported the palladium catalyzed *ortho*-C-H arylation utilizing a variety of directing groups. In this investigation they reported the use of a pyrrolidinone, acetanilide and oxazolidinone aniline derivatives as chelating groups (Scheme 2).⁸

Scheme 2 Palladium Catalyzed *ortho*-C-H Arylation of Pyrrolidinone Derivatives

In 2010, Dong co-workers reported the *ortho*-arylation of *N*-substituted anilines using benzene as the coupling partner, in an attractive oxidative coupling process (Scheme 2a). When moving away from benzene to other aromatics such as anisole, selectivity issues were shown to be present. However the major products shown in these examples had C-H activation taking place at the *para*-position to the arene functionality.⁹ The same group also applied this to the *ortho*-arylation of *N*-aryloxazolidinones.¹⁰ This methodology was further developed by Yu and co-workers where they found the addition of a pyridine based ligand enabled selective *para*-substitution on the arene coupling partner.¹¹ In the same year as Dong's original report, Lipshutz and co-workers reported the *ortho*-arylation of aniline derivatives furnished with a urea directing group (Scheme 2b). They utilized aryl boronic acids as coupling partners in this wide-scoped chemistry. Unfortunately, they found that mono and di-*ortho*-C-H functionalization selectivity issues were observed with *para*-substituted structures.¹²

Scheme 3 Palladium Catalyzed *ortho*-C-H Arylation of Aniline Derivatives

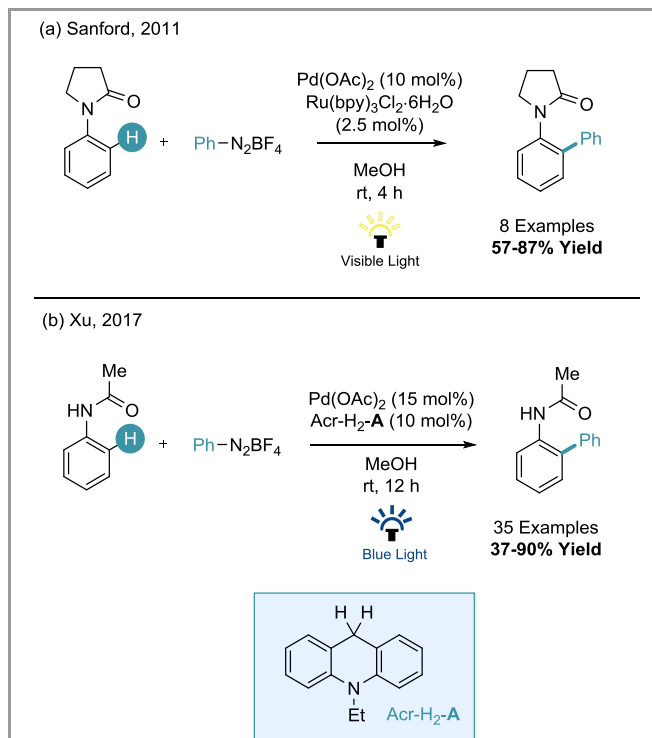
In 2011, Wu and co-workers described the *ortho*-arylation of *N*-pyridylanilines using ArBF_3K salts as coupling partners.¹³ Here they showed that under the reaction conditions they formed the *ortho*-C-H arylated product (A, Scheme 4). They also isolated the carbazole structure (B), formed via in situ N-C bond construction. The ratios of these products were prone to variation from almost 1:1 to roughly 2:8. These transformations manifest the power of palladium catalysis to undergo cascade C-H functionalization reactions to build up complexity rapidly. The same group then developed this methodology further to enable selective mono-arylation and subsequent selective carbazole formation.¹⁴

Scheme 4 Palladium Catalyzed *ortho*-Arylation of Aniline Derivatives Furnished with a Pyridine Directing Group and *in situ* Carbazole Formation

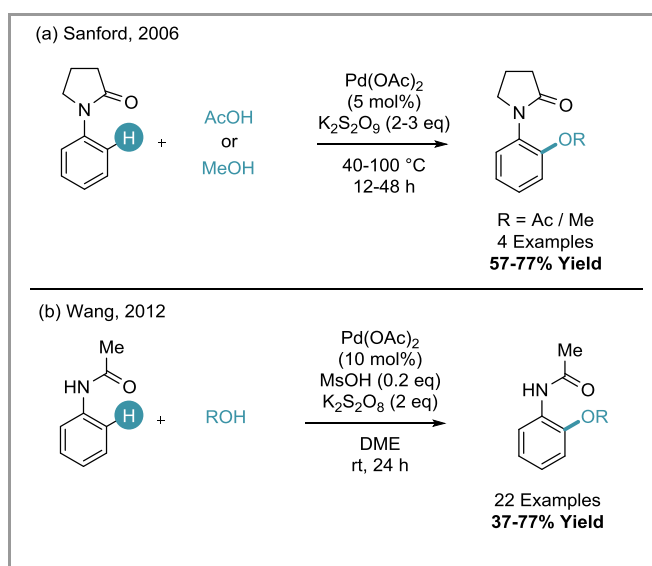
Combining photoredox catalysis and traditional cross coupling chemistry has the potential to unlock new synthetic transformations as well as enabling milder reaction conditions.¹⁵

In 2011, Sanford and co-workers developed the dual photoredox / C-H activation catalysis system with a $\text{Ru}(\text{bpy})_3\text{Cl}_2$ / $\text{Pd}(\text{OAc})_2$ catalyst couple. This enabled the use of aryl diazonium salts in *ortho*-arylation chemistry using visible light at room temperature (Scheme 5a). As with their previous reports, a multitude of directing groups were employed including the aniline based pyrrolidinone. The authors proposed a dual catalyst cycle with palladium and ruthenium catalysts working in synergy to produce the *ortho*-arylated products.¹⁶ This work was expanded on by Xu in a recent report where a

variety of anilides were employed in a dual organophotoredox / palladium C-H activation cycle (Scheme 5b).¹⁷

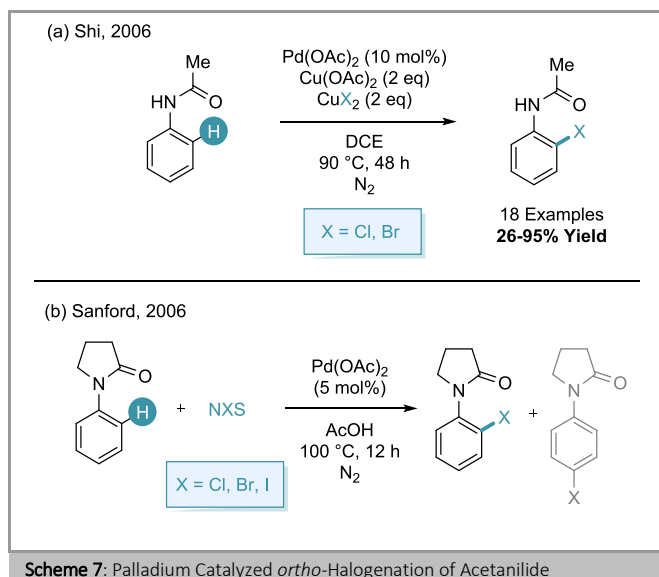
Scheme 5 Photoredox / Palladium Catalyzed *ortho*-C-H Arylation of Aniline Derivatives

In 2006, Sanford and co-workers developed the *ortho*-C-H oxygenation of a variety of arenes. This chemistry enabled both C-H acetoxylation and C-H alkoxylation using a variety of directing groups, including pyrrolidinone (Scheme 6a).¹⁸ This work was further developed by Wang and co-workers to utilize acetanilide directing groups and a wider range of alcohol coupling partners (Scheme 6b).¹⁹

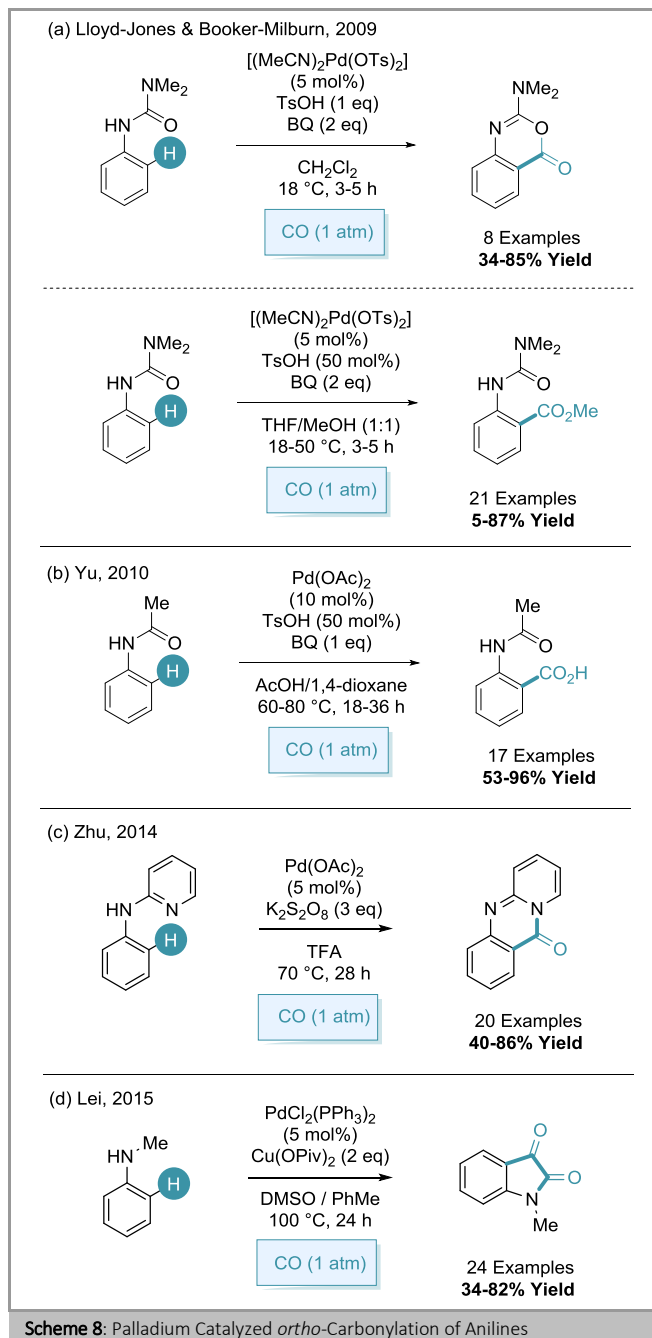
Scheme 6 Palladium Catalyzed *ortho* Alkoxylation/Acyloxylation of Anilide Derivatives

In 2006 Shi and co-workers reported the *ortho*-C-H halogenation of acetanilide derivatives. Here they utilized

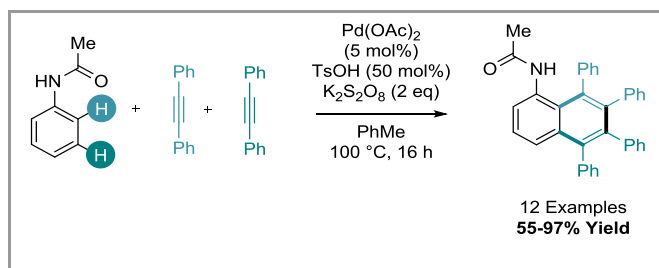
palladium acetate and copper halide salts to enable efficient and selective C-H chlorination and bromination reactions (Scheme 7a). As acetanilide is an electron rich *ortho/para* director, substrates were often biased to disfavour any competing *para*-functionalization.²⁰ Sanford and co-workers later that year reported a full investigation into mechanistic aspects behind the *ortho/para* competition (Scheme 7b).²¹ Bedford and co-workers later added to this investigation, exploring solvent-free palladium catalysis and how this impacts the regioselectivity observed.²²



The carbonylative palladium catalyzed cross coupling has become a ubiquitous transformation in the synthetic toolbox. This methodology was first applied to C-H activation of aniline derivatives by Lloyd-Jones, Booker-Milburn and co-workers in 2009.²³ Here they employed a urea directing group with palladium acetate in a CO atmosphere, which was shown to cyclize to form the oxazinone ring, and the carboxy ester when using an alcoholic co-solvent (Scheme 8a). Yu and co-workers described the use of this chemistry in an *ortho*-C-H carboxylation reaction (Scheme 8b). Here they found that the use of acetanilide directing group and the use of acetic acid as co-solvent gave the free carboxylic acid product (with no cyclization).²⁴ This carbonylative C-H activation methodology has also been employed by Zhu and co-workers showing that a pyridine directing group led to cyclization to form the pyrimidine-4-one ring (Scheme 8c).²⁵ In 2015, Lei and co-workers disclosed the elegant transformation of *N*-alkylanilines into isatins *via* a double carbonylation to form the 5-membered ring (Scheme 8d).²⁶

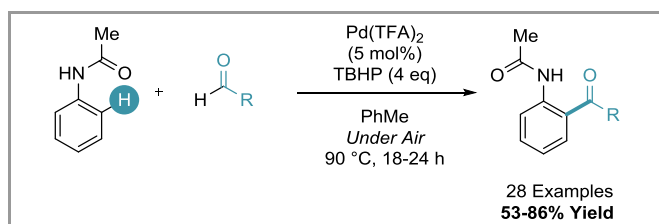


In 2010, Cui and Wu and co-workers described the palladium catalyzed synthesis of naphthalenes from acetanilides using direct ring construction using two equivalents of alkyne coupling partner (Scheme 9).²⁷ This enabled the C-H activation of both *ortho* and *meta*-C-H bonds, where the cascade reaction was shown to be efficient with symmetrical diarylalkynes. This chemistry was expanded upon by Zhang and co-workers who displayed under complementary rhodium catalysis, the anilide directing group could undergo *in situ* removal resulting in a traceless directing group strategy.²⁸



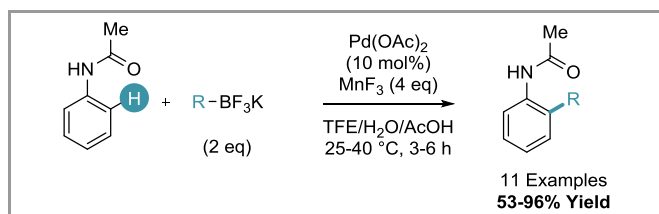
Scheme 9 Palladium Catalyzed *ortho*-/*meta*-Annulation of Anilide Derivatives

In 2011, Kwong and co-workers reported the *ortho*-acylation of acetanilide derivatives utilizing Pd(TFA)₂ as the catalyst and TBHP as oxidant (Scheme 10). This transformation was shown to offer wide scope with a variety of arenes and aryl and alkyl aldehyde coupling partners undergoing this chemistry.²⁹



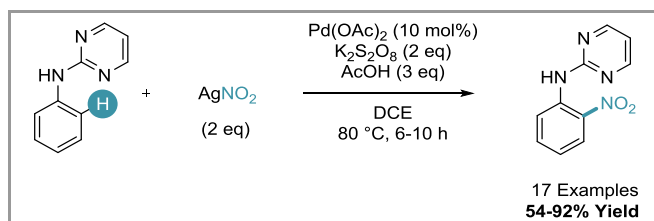
Scheme 10 Palladium Catalyzed *ortho*-C-H Acylation of Anilide Derivatives

In 2013 Sanford and co-workers described the use of alkyl-trifluoroborate salts in the *ortho*-alkylation of anilides (Scheme 11). They described the key use of MnF₃ as an oxidant and a carefully designed solvent mixture to maximize reaction efficiency.³⁰ It must be noted that this methodology will be mechanistically similar to that described above by Lipshutz and co-workers.¹²



Scheme 11 Palladium Catalyzed *ortho*-C-H Alkylation of Anilides using Trifluoroborate Salts

In 2016, Kapur and co-workers developed the use of *N*-pyrimidinylanilines in *ortho*-C-H nitration methodology using silver nitrite as the nitro source (Scheme 12). They did however find competing *para*-SeAr nitration in some examples.³¹

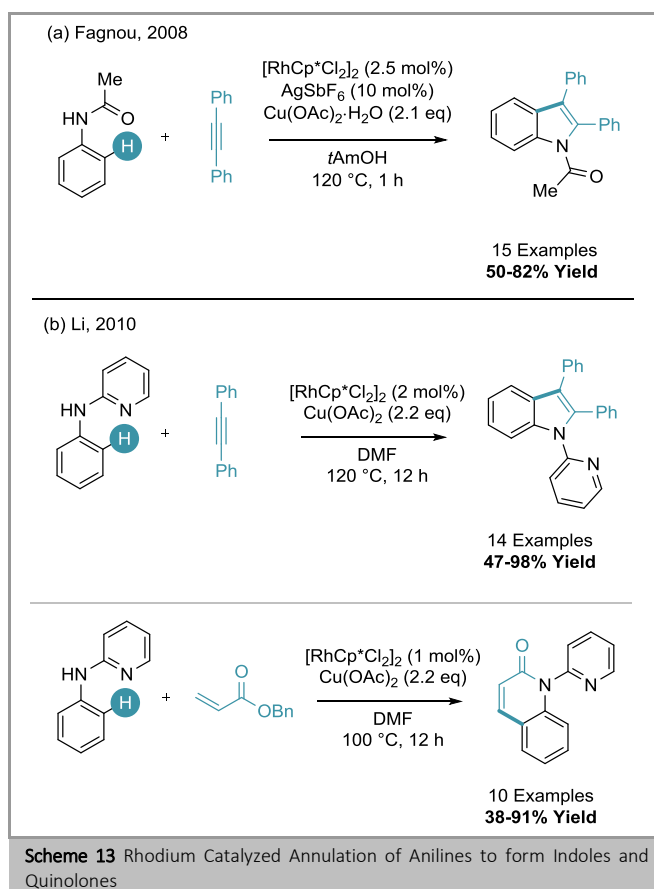


Scheme 12 Palladium Catalyzed *ortho*-C-H Nitration of *N*-pyrimidinylanilines

2.2: Rhodium

Rhodium catalyzed C-H functionalization has become a powerful asset to the synthesis of a wide range of biologically relevant structures and building blocks.³²

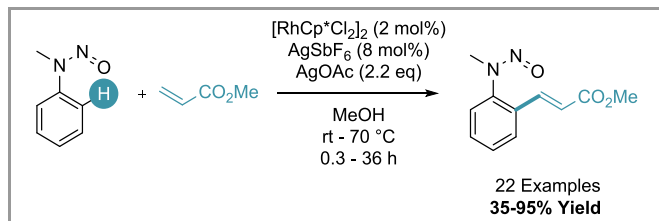
In 2008, Fagnou and co-workers were the first to apply rhodium catalysis to the derivation of aniline structures. Here they utilised an anilide directing group in an annulation reaction with acetylenes (Scheme 13a). This chemistry led to the formation of C2 / C3 di-substituted indole derivatives.³³ This work was followed by a report from Li and co-workers who reported the annulation of pyridyl-anilines with acetylenes (Scheme 13b) and α,β -unsaturated esters (Scheme 13c).³⁴ This catalysis was shown to lead to cyclization at the ester position to give the quinolone structure, with some selectivity issues when using unsymmetrical arenes.



Scheme 13 Rhodium Catalyzed Annulation of Anilines to form Indoles and Quinolones

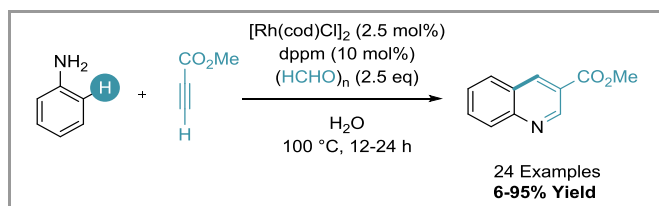
N-nitrosoanilines have been shown as versatile substrates for C-H functionalization methodology. In 2013, Zhu and co-workers reported the rhodium catalyzed *ortho*-alkenylation of *N*-nitrosoaniline. This reaction was shown to be widespread and the nitroso directing group remaining intact (Scheme 14).³⁵ *N*-

nitrosoanilines have also been applied in *ortho*-cyanation,³⁶ annulation (rhodium/cobalt catalyzed),³⁷ acetoxylation,³⁸ and acylation³⁹ chemistry (both palladium catalyzed).



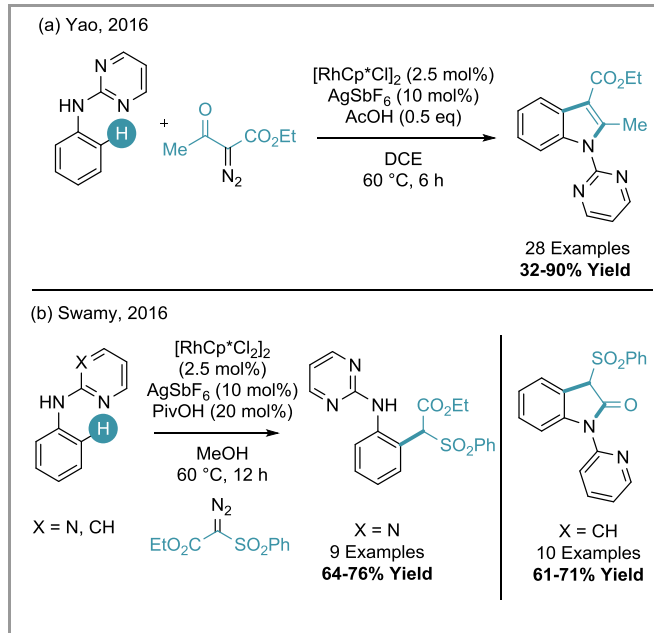
Scheme 14 Rhodium Catalyzed *ortho*-C-H alkenylation of *N*-nitrosoaniline derivatives

Up to this point all of the methods discussed in the regioselective C-H functionalization have utilized some form of *N*-substitution. Despite this, in 2015, Balaraman and co-workers reported the rhodium catalyzed annulation of free aniline with an alkyne coupling partner and a carbon equivalent (in *para*-formaldehyde) which enabled the construction of quinoline structures (Scheme 15). Despite the mechanistic complexity and potential for multiple by-products this methodology was shown to be wide scope and predominantly high yielding.⁴⁰



Scheme 15 Rhodium Catalyzed Annulation of Anilines to Form Quinolines

Rhodium catalysis has been universal to promoting metalcarbenoid chemistry.⁴¹ There has been interest in combining these methods with C-H activation. In 2016 Yao and co-workers achieved this in the rhodium catalyzed coupling of pyrimidinylanilines and α -diazo esters, to form the C-H alkylated products (Scheme 16a).⁴² Swamy and co-workers also disclosed similar chemistry finding pyridylanilines underwent an *in situ* lactamization to form the oxindole structures (Scheme 16b).⁴³



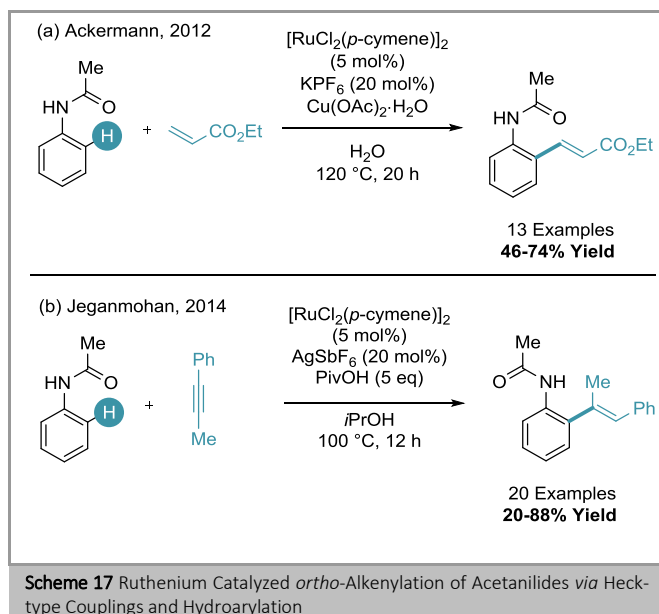
Scheme 16 Rhodium Catalysed Indole Formation Using Diazo Esters

2.3: Ruthenium

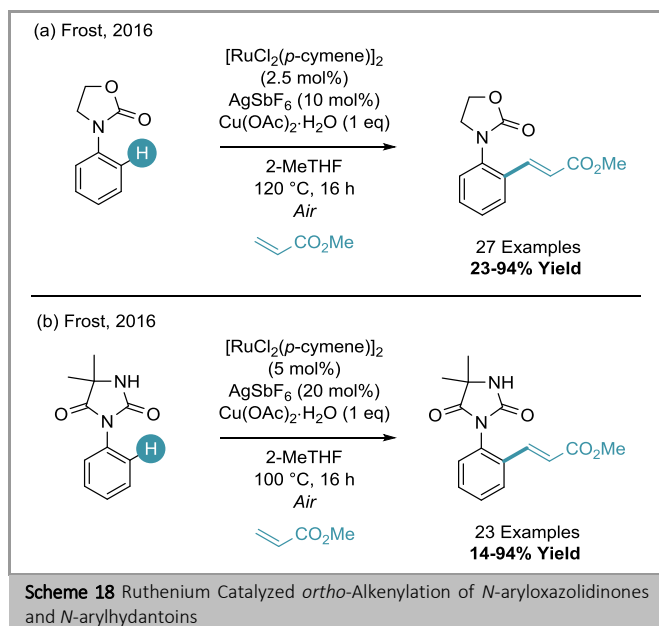
Ruthenium catalyzed C-H functionalization has received substantial interest in recent years, due to its low-cost cf. palladium, iridium, and rhodium, as well as lower toxicity profiles, higher abundance and the potential to unlock unique chemical reactivity.⁴⁴

The *ortho*-C-H functionalization of arenes using weakly coordinating directing groups has been explored heavily using ruthenium catalysis with pioneering contributions from Ackermann⁴⁵ and Jeganmohan.^{46,5b}

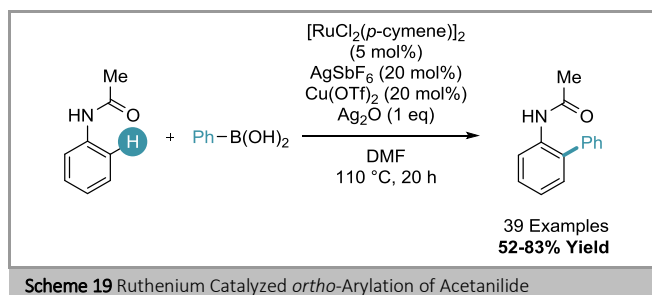
In 2012, Ackermann and co-workers utilized acetanilide substrates in *ortho*-alkenylation chemistry. This work was also shown to react efficiently using KPF₆ as co-catalyst and with water as solvent (Scheme 17a). This is an attractive feature in C-H activation chemistry as often high boiling polar aprotic solvents are used. This methodology was limited to electron deficient alkene coupling partners.⁴⁷ By switching from a basic to an acidic environment, Jeganmohan achieved a complementary hydroarylation reaction which enabled installation of electron rich alkene substituents (Scheme 17b).⁴⁸ Jeganmohan has also reported a development of Ackermann's alkenylation chemistry however in this case carrying out the oxidative C-H functionalization leaving only hydrogen gas as a by-product.⁴⁹



In 2016, Frost and co-workers disclosed two reports on the *ortho*-alkenylation of arenes using the biologically relevant oxazolidinone and hydantoin heterocycles as directing groups. This chemistry was shown to be amenable to a wide variety of arenes, and amino acid derived oxazolidinone and hydantoin heterocycles (Scheme 18).⁵⁰



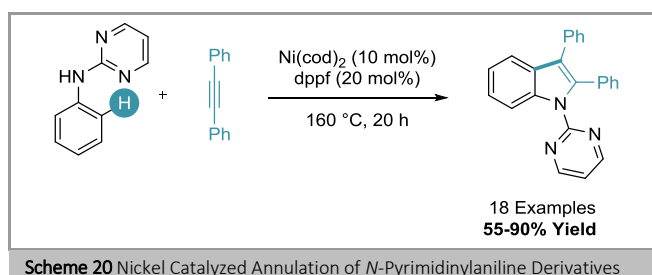
Ackermann and co-workers also showed that under similar conditions to their work above they could achieve an *ortho*-C-H arylation reaction of acetanilides using aryl boronic acid coupling partners (Scheme 19). This chemistry was shown to tolerate a vast array of anilides and boronic acid coupling partners without detriment to yield.⁵¹



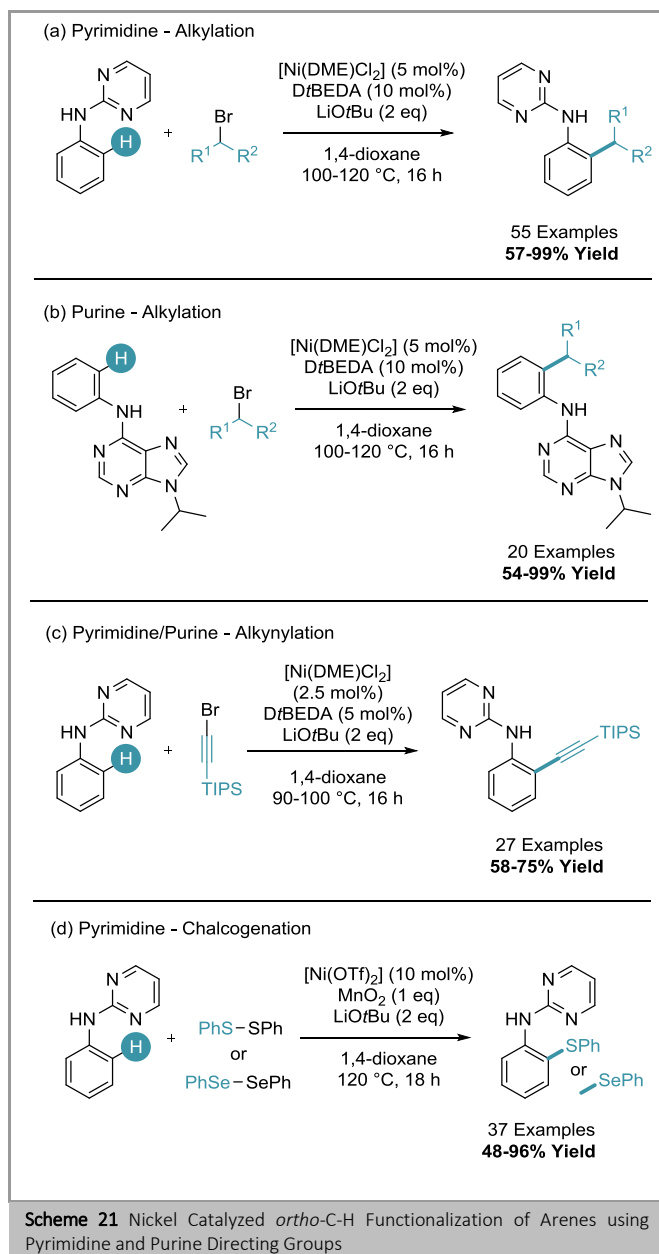
2.4: Nickel

The use of base metals in cross coupling and C-H activation chemistry has come to the forefront of recent developments in catalysis. Due to the innate similarities with palladium, nickel has emerged as a vital candidate in the pursuit of greener catalysis systems.⁵²

Ackermann and co-workers employed nickel(0) catalysis in the annulation of *N*-pyrimidinylanilines to give substituted indoles (Scheme 21). This transformation has been discussed previously, however the authors have provided the most sustainable route with respect to catalyst.⁵³



Ackermann has since followed this seminal report on the C-H functionalization of anilines using nickel catalysis with a number of other innovative applications. The first of these demonstrates the *ortho*-alkylation of anilines furnished with a pyrimidine directing group in excellent yields and with a huge number of examples (Scheme 21a). Here they suggest an *ortho*-nickelated complex can generate alkyl radicals via a single electron transfer mechanism, with a Ni(II)/(Ni(III)) oxidation state change.⁵⁴ In 2017 the group applied this chemistry to the *ortho*-alkylation of purine derivatives, applying this to the derivation of nucleosides and the formation of potential fluorescence probes (Scheme 21b).⁵⁵ The same group also found that under identical conditions they could couple bromoalkynes with both pyrimidine and purine directing groups in good yields (Scheme 21c).⁵⁶ In 2016 they found that their nickel system could also be applied to the chalcogenation of aniline derivatives installing sulfide and selenide functionality (Scheme 21d).⁵⁷



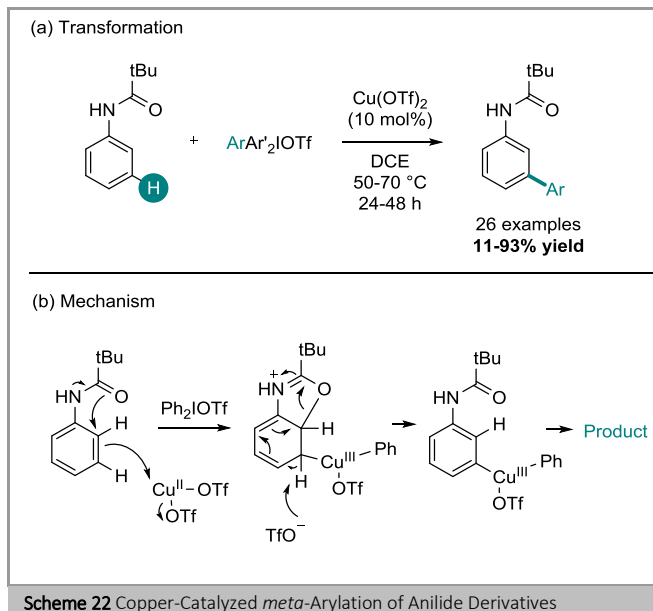
3: *Meta*-Selective C-H Functionalization of Anilines

In order to move beyond the scope of *ortho*-selectivity, new synthetic methodologies have been designed to grant access to *meta*-selective C-H functionalization. These synthetic techniques have relied on three main methods; template directing groups, transient mediator chemistry and σ -activation. All three of these important methods have been applied to the *meta*-functionalization of aniline derivatives and will be discussed in this review, with a particular focus on the mechanism involved in these chemistries.⁴

Meta-selective C-H functionalization has been an area of great interest in recent years due to the synthetic potential it holds in complete control of regioselectivity in C-H activation chemistry. As an innate *ortho* / *para* director the ability to access selective *meta*-C-H functionalization of anilines could provide a vital synthetic tool in future developments.

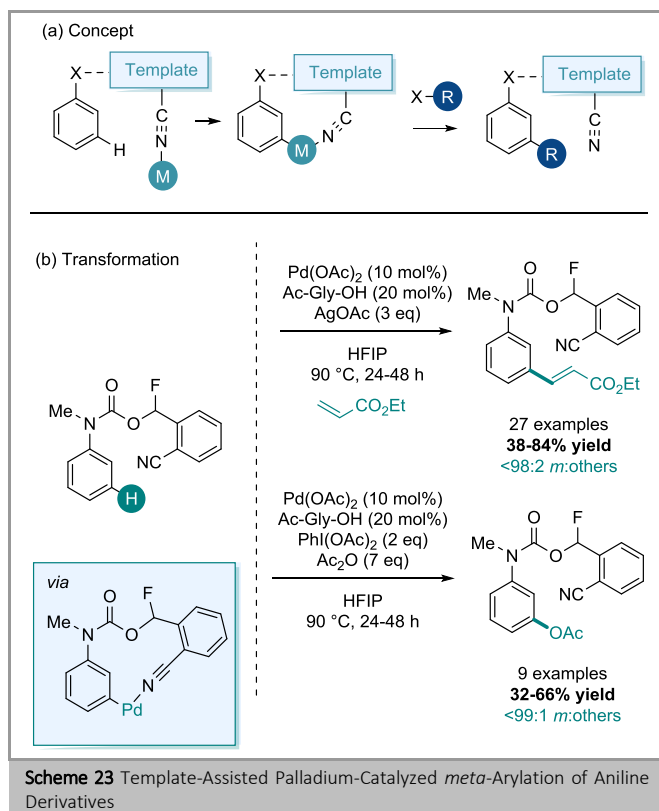
In 2009, Gaunt and co-workers disclosed a pioneering report in remote functionalization methodology on the *meta*-arylation of anilides using arylodonium reagents (Scheme 22a). Here they

used pivanilide as a model substrate, which they proposed could undergo electrophilic cupration through a conjugate addition-style system through the benzene ring (Scheme 22b).⁵⁸ They then suggested rearomatization and oxidative addition of the hypervalent iodine coupling partner would give them a *meta*-cuprated arene. This structure could then form the C-C bond through traditional reductive elimination chemistry.

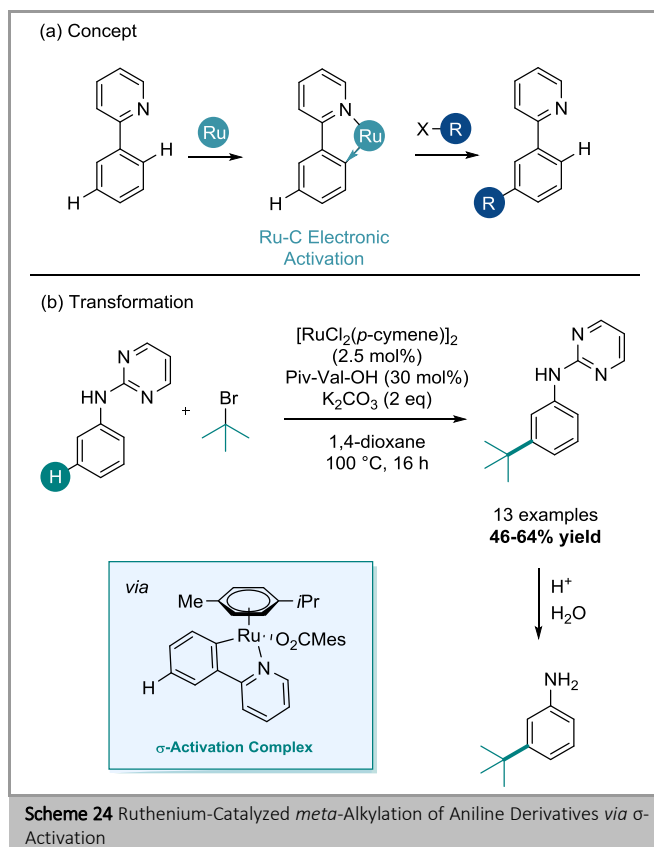


The use of templated directing groups which selectively cyclometalate at the *meta*-position has become a widespread and well-researched area of remote functionalization (Scheme 23a).^{4d,59}

Yu and co-workers applied their templated directing group methodology to aniline derivatives in 2014. They demonstrated that this concept was applicable to *meta*-C-H alkenylation and *meta*-C-H acetoxylation reactions (Scheme 23b). They proposed a 12-membered metallacycle which can then undergo C-H functionalization.⁶⁰ In a following report they also applied this concept to the selective *meta*-functionalization of indoline derivatives at the C6 position.⁶¹



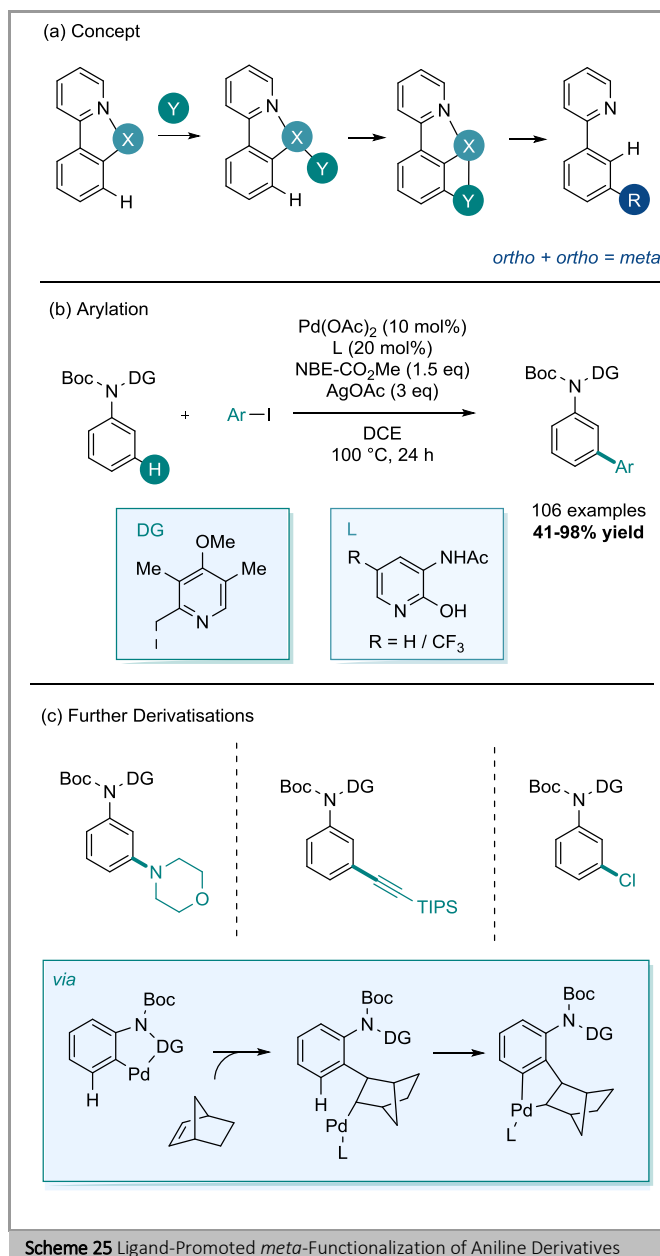
Ackermann and co-workers reported the *meta*-alkylation of aniline derivatives via a σ -activation process.⁶² Ruthenium catalyzed σ -activation focuses on the concept of using stable and planar ruthenacycles as transient electronic *para*-directors (Scheme 24a). This can be used with anilines to override the inherent predisposition to react at the *ortho* and *para* positions. They propose that a single electron transfer process enables the formation of tertiary alkyl radicals which then interact with the arene (Scheme 24b).⁶³ It must be noted that this selectivity is complementary to their report discussed above under nickel catalysis.⁵⁴



Another method that has been used to access remote *meta*-functionalization is the use of a transient mediator. This concept uses an *ortho*/*ortho*-functionalization to give net *meta*-functionalization (Scheme 25a).

In 2016 Yu and co-workers coupled this concept with the Catellani reaction⁶⁴ in a *meta*-arylation reaction using anilines furnished with a specialized pyridine auxiliary (Scheme 25b).⁶⁵ With regards to mechanism they used directed cyclopalladation *ortho* to the acetamide directing group, which then allowed norbornene coordination and migratory insertion, to give the Catellani-type intermediate. This then enables cyclopalladation in the *meta* C–H bond, and subsequent oxidative addition / reductive elimination gives the C–H functionalised intermediate. Protodemetalation then takes place to give the *meta* substituted arene.

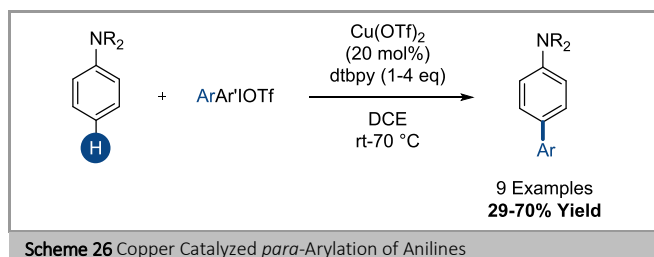
The same group then applied these same bespoke anilines to *meta*-amination,⁶⁶ alkylation,⁶⁶ and chlorination⁶⁷ methodologies (Scheme 25c).



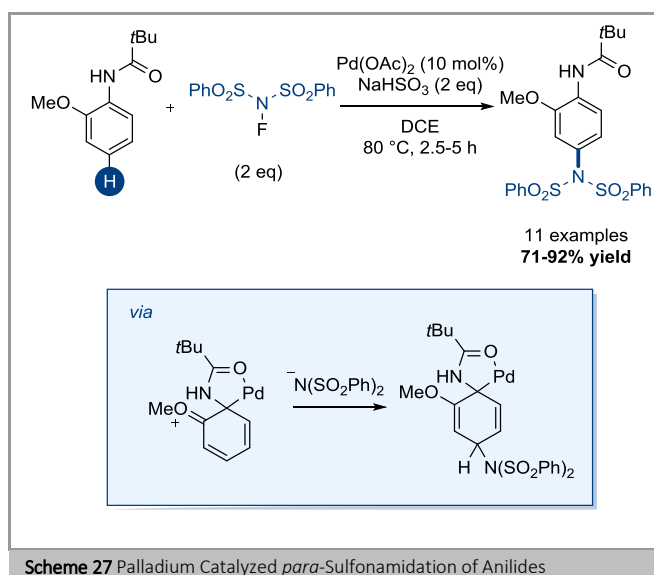
4: Para-Selective C-H Functionalization of Anilines

The ability to go further beyond *meta*-selectivity to *para*-selective C-H functionalization relies less heavily on metal chelating directing groups and more on electronic and steric effects.^{4b} Despite this, there have been examples of the careful manipulation of extended directing groups.⁶⁸ As a strongly electron donating group, anilines have become widely studied model substrates in this chemistry, and the contributions to this date will be explored.

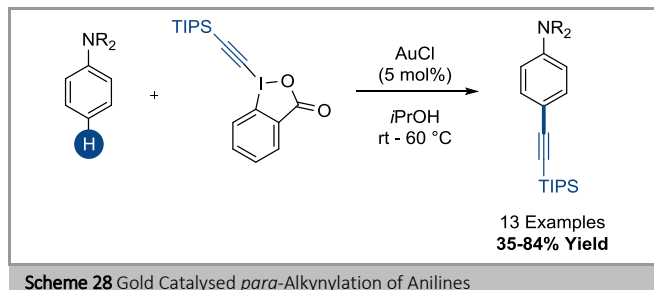
The first example of transition metal catalyzed *para*-C-H functionalization of aniline derivatives came from the Gaunt lab in 2011. Here they described the copper-catalyzed *para*-C-H arylation of anisole and aniline derivatives using hypervalent iodine salts (Scheme 26).⁶⁹ Surprisingly, at slightly higher temperatures this reaction was shown to proceed in the absence of a copper catalyst.



Shortly after this initial work by Gaunt, Zhang and co-workers reported the *para*-sulfonimidation of anilide derivatives. Using *N*-fluorobenzenesulfonimide (NFSI) as a coupling partner they showed using *ortho*-methoxy anilides they could enable selective *para*-C-H functionalization (Scheme 27). With regards to mechanism they propose an electrophilic cyclopalladation at the *ipso*-position using the methoxy as a non-innocent arene substituent.⁷⁰

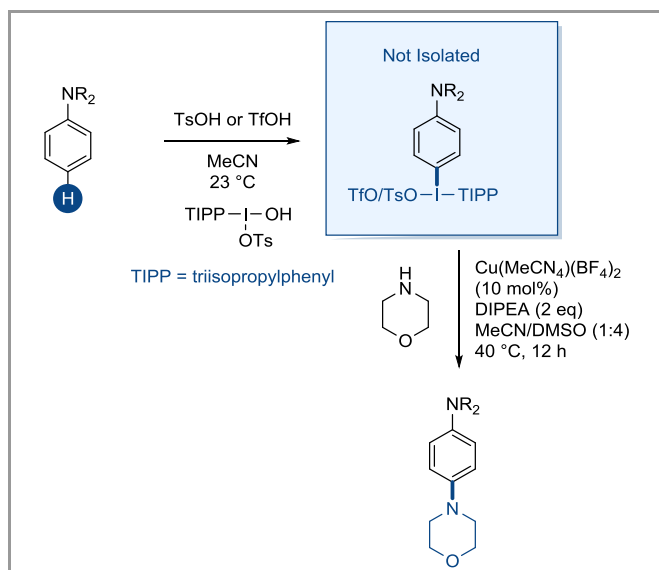


In 2012, Waser and co-workers applied gold catalysis to the *para*-alkynylation of aniline derivatives using hypervalent iodine reagents (Scheme 28). This was shown to be incredibly selective for the *para*-position and a modest scope of aniline derivatives was reported by the authors.⁷¹



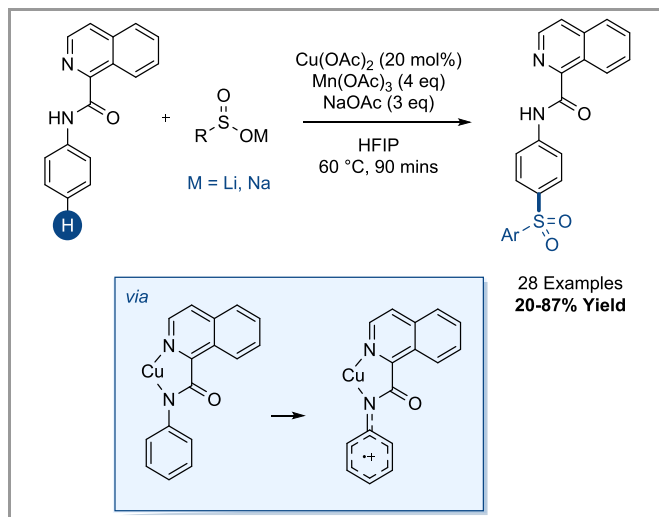
In 2015, Suna and co-workers reported the *para* amination of electron rich arenes. This was achieved by using an electrophilic iodination selectively at the *para* position which can then undergo copper catalyzed Ullmann cross coupling chemistry to give the *para*-aminated structure (Scheme 29). They applied this concept to pyrrolidinone substituted arenes and oxazolidinones, where they demonstrated the application of this

methodology to the total synthesis of oxazolidinone-based antibacterial linezolid.⁷²



Scheme 29 Electrophilic Iodination / Copper Catalyzed Coupling Relay in the *para*-C-H Functionalization of Anilines

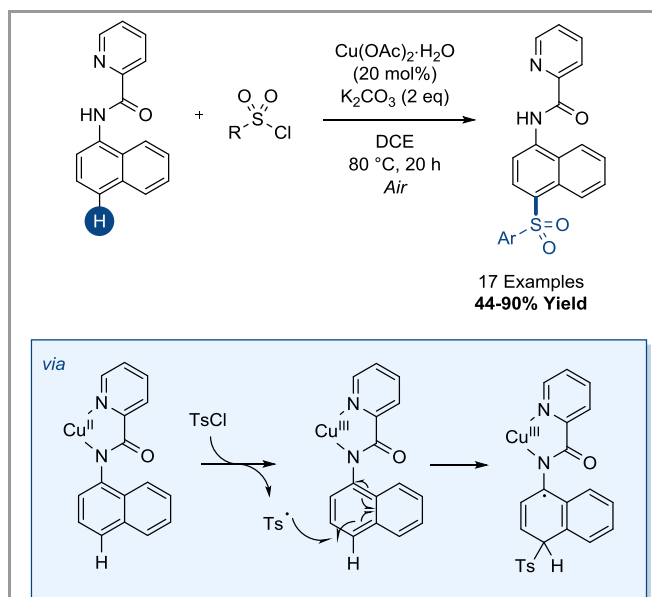
Recently there have been two reports on the use of cyclocuprated species in the *para*-functionalization of aniline derivatives. The first of these came from Manolikakes and co-workers on the *para*-sulfonation of bespoke anilide derivatives.⁷³ Here they suggested that a cyclocuprated structure could enable single electron transfer with the arene. This radical cation arene could then interact with sulfonyl radicals formed *via* interaction between the stoichiometric manganese oxidant and the sulfinate salts (Scheme 30).



Scheme 30 Copper-Catalyzed *para*-Sulfonation of Anilides

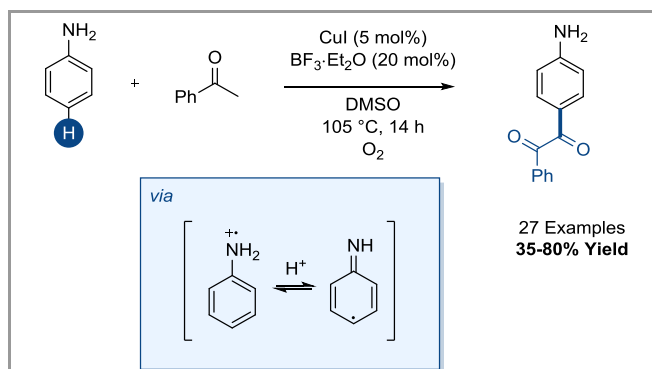
The second of these examples also utilizes copper redox catalysis. However, Weng and Lu and co-workers report the use of a cyclocuprated structure which can form tosyl radicals itself *via* single electron transfer (Scheme 31).⁷⁴ They applied this concept to the *para*-sulfonation of 2-aminonaphthalene derivatives. The authors also demonstrated the unoptimized *para*-selective acetoxylation, bromination, iodination,

sulfonimidation, and trifluoromethylation of 2-aminonaphthalene derivatives.



Scheme 31 Copper Catalyzed *para*-Sulfonation of Aminonaphthalene Derivatives

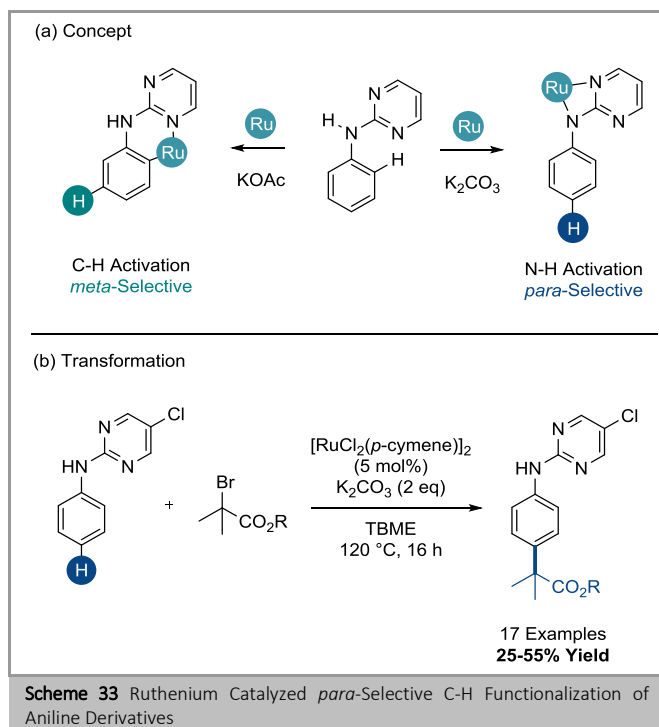
As with *ortho* and *meta*-C-H functionalization the ability to carry out selective C-H functionalization of unsubstituted aniline has proved challenging. Despite this, Deng and co-workers reported the *para*-acylation of free aniline using copper catalysis (Scheme 32). They suggest a mechanism using copper redox catalysis to generate the anilino radical *in situ* which can then interact with acetophenone *via* its enol tautomer. They then suggest that aerobic redox oxygenation takes place at the benzyl position to give the diketone structure.⁷⁵



Scheme 32 Copper Catalyzed *para* Oxalation of Aniline

In 2017, Frost and co-workers reported the *para*-C-H alkylation of aniline derivatives utilizing a radical protocol.⁷⁶ The authors suggest that an N-H activated complex can form (similar to Weng and Lu,⁷³ and Manolikakes⁷⁴) rather than a C-H activated complex (similar to Ackermann⁶³) in Ru-C σ -activation methodology (Scheme 33a). They then suggest that this organometallic species can undergo radical functionalization at the *para* position *cf. meta* with the work of Ackermann and co-workers. The transformation was shown to take place with tertiary α -halocarbonyl coupling partners in modest yields

(Scheme 33b). DFT studies also validated the base dependent switch in energy barriers between N-H activation and the complementary C-H activation.



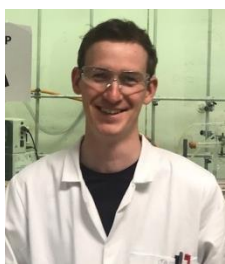
5. Conclusion

Anilines are a vital structure in organic synthesis, present in a wide range of biologically relevant structures. Due to this the development of anilines as C-H activation templates has received an influx of new methodologies in recent years. These innovative processes have enabled the selective *ortho* (predominated by traditional directing group chemistry), *meta* (applying modern remote functionalization techniques), and *para* (manipulating electronic effects) functionalization of a variety of aniline structures. The advancement of regioselective C-H functionalization will continue to grow rapidly, and break through from proof of concept methodology to mainstream synthesis, and it is undoubted that anilines will play a vital role in that development.

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